

# Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis

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## ABSTRACT

**Objective** To conduct a comprehensive systematic review and meta-analysis of studies assessing the effect of alcohol consumption on multiple cardiovascular outcomes.

**Design** Systematic review and meta-analysis.

**Data sources** A search of Medline (1950 through September 2009) and Embase (1980 through September 2009) supplemented by manual searches of bibliographies and conference proceedings.

**Inclusion criteria** Prospective cohort studies on the association between alcohol consumption and overall mortality from cardiovascular disease, incidence of and mortality from coronary heart disease, and incidence of and mortality from stroke.

**Studies reviewed** Of 4235 studies reviewed for eligibility, quality, and data extraction, 84 were included in the final analysis.

**Results** The pooled adjusted relative risks for alcohol drinkers relative to non-drinkers in random effects models for the outcomes of interest were 0.75 (95% confidence interval 0.70 to 0.80) for cardiovascular disease mortality (21 studies), 0.71 (0.66 to 0.77) for incident coronary heart disease (29 studies), 0.75 (0.68 to 0.81) for coronary heart disease mortality (31 studies), 0.98 (0.91 to 1.06) for incident stroke (17 studies), and 1.06 (0.91 to 1.23) for stroke mortality (10 studies). Dose-response analysis revealed that the lowest risk of coronary heart disease mortality occurred with 1–2 drinks a day, but for stroke mortality it occurred with  $\leq 1$  drink per day. Secondary analysis of mortality from all causes showed lower risk for drinkers compared with non-drinkers (relative risk 0.87 (0.83 to 0.92)).

**Conclusions** Light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes.

## INTRODUCTION

Possible cardioprotective effects of alcohol consumption seen in observational studies continue to be hotly debated in the medical literature and popular media. In

the absence of clinical trials, clinicians must interpret these data when answering patients' questions about taking alcohol to reduce their risk of cardiovascular disease. Systematic reviews and meta-analyses have addressed the association of alcohol consumption with cardiovascular disease outcomes<sup>1–8</sup> but have not uniformly addressed associations between alcohol use and mortality from cardiovascular disease, as well as the incidence and mortality from coronary heart disease and stroke. Additionally, further studies have been published since 2006, when the most recent reviews appeared. The continuing debate on this subject warrants an in depth reassessment of the evidence.

In this paper, we synthesise results from longitudinal cohort studies comparing alcohol drinkers with non-drinkers for the outcomes of overall mortality from cardiovascular disease, incident coronary heart disease, mortality from coronary heart disease, incident stroke, and mortality from stroke. Because of the many biological effects of alcohol consumption, we also examine the association of alcohol with mortality from all causes when this is reported in studies. We conducted meta-analyses for each of these outcomes and a sensitivity analysis with lifetime abstainers as the reference category to account for the heterogeneity within the reference group of non-drinkers. We also examined the effect of confounding on the strength of observed associations. In our companion paper,<sup>10</sup> we link these cardiovascular outcomes with experimental trials of alcohol consumption on candidate causal molecular markers.

## METHODS

### Data sources and searches

We performed a systematic review and meta-analysis following a predetermined protocol in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.<sup>9</sup> We identified all potentially relevant articles regardless of language by searching Medline (1950 through September 2009) and Embase (1980 through September

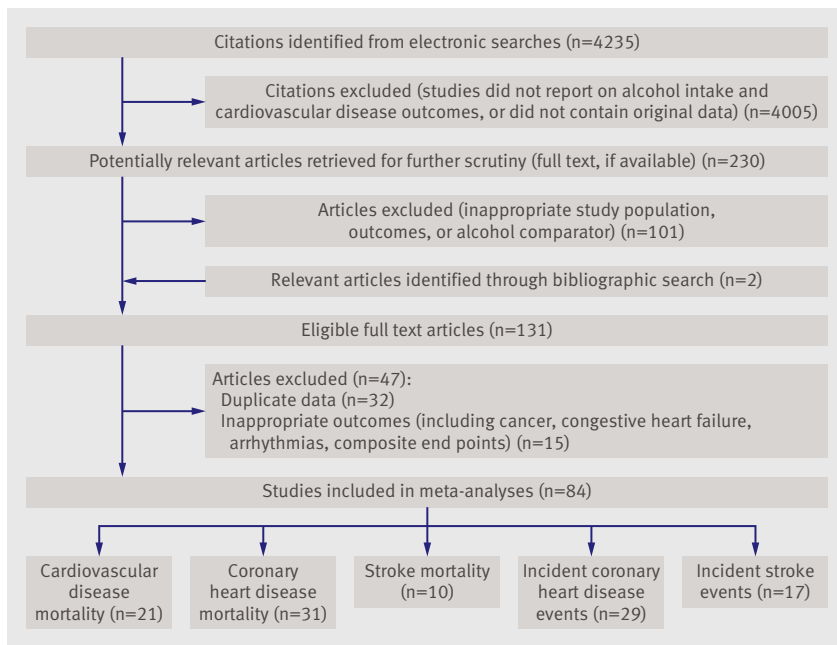


Fig 1 | Details of study selection for review

2009). Searches were enhanced by scanning bibliographies of identified articles and review articles, as well as reviewing conference proceedings from three major scientific meetings (American Heart Association, American College of Cardiology, and European Heart Congress) between 2007 and 2009. Experts in the field were contacted regarding missed, ongoing, or unpublished studies.

To search electronic databases, we used the strategy recommended for systematic reviews of observational studies.<sup>10</sup> We specified three comprehensive search themes:

- To identify relevant terms related to the exposure of interest (theme 1), the first Boolean search used the term “or” to explode (search by subject heading) and map (search by keyword) the medical subject headings “ethanol” or “alcohol” or “alcoholic beverages” or “drinking behaviour” or “alcohol drinking” or text words “drink\$” or “liquor\$” or “ethanol intake” or “alcohol\$ drink\$” or “ethanol drink\$”
- To identify relevant outcomes (theme 2), a second Boolean search was performed using the term “or” to explode and map the medical subject headings “stroke” or “cardiovascular diseases” or “myocardial infarction” or “myocardial ischemia” or “coronary artery disease” or “heart infarction” or text words “cva\$” or “infarct\$” or “ischem\$” or “cvd” or “ami” or “ihd” or “cad”
- To identify relevant study designs (theme 3), a final Boolean search using the term “or” to explode and map the medical subject headings “cohort studies” or “follow-up studies” or “incidence” or “prognosis” or “early diagnosis”

or “survival analysis” or text words “course” or “predict\$” or “prognos\$” was performed.

These three comprehensive search themes were then combined using the Boolean operator “and” in varying combinations.

### Study selection

Two individuals (SEB and PER) independently reviewed all identified abstracts for eligibility. All abstracts reporting on the association between alcohol intake and cardiovascular disease events were selected for full text review. This stage was intentionally liberal. We discarded only those abstracts that clearly did not meet the aforementioned criteria. The inter-rater agreement for this review was high ( $\kappa=0.86$  (95% confidence interval 0.80 to 0.91)). Disagreements were resolved by consensus.

The same reviewers performed the full text review of articles that met the inclusion criteria and articles with uncertain eligibility. Articles were retained if they met the inclusion criteria for study design (prospective cohort design), study population (adults  $\geq 18$  years old without pre-existing cardiovascular disease), exposure (current alcohol use with a comparison group of non-drinkers), and outcome (overall cardiovascular disease mortality or atherothrombotic conditions, specifically incident coronary heart disease, coronary heart disease mortality, incident stroke, or stroke mortality). Both published and unpublished studies were eligible for inclusion. Authors were contacted if the risk profile of the cohort was unclear.

### Data extraction and quality assessment

The primary exposure variable was the presence of active alcohol drinking at baseline compared with a reference group of non-drinkers. Because of the heterogeneity of this reference group, we identified the subset of studies using lifetime abstainers as the reference group and studies that distinguished former drinkers from non-drinkers. Whenever available, we extracted information on amount of alcohol consumed, using grams of alcohol per day as the common unit of measure. When a study did not specifically report the grams of alcohol per unit, we used 12.5 g/drink for analysis.<sup>11</sup> We standardised portions as a 12 oz (355 ml) bottle or can of beer, a 5 oz (148 ml) glass of wine, and 1.5 oz (44 ml) glass of 80 proof (40% alcohol) distilled spirits. Volume of intake was categorised as  $<2.5$  g/day ( $<0.5$  drink), 2.5–14.9 g/day (about 0.5–1 drink), 15–29.9 g/day (about 1–2.5 drinks), 30–60 g/day (about 2.5–5 drinks), and  $>60$  g/day ( $\geq 5$  drinks).

The outcome variables of interest were defined as the presence or absence of death from cardiovascular disease (that is, fatal cardiovascular or stroke events), incident coronary heart disease (fatal or non-fatal incident myocardial infarction, angina, ischaemic heart disease, or coronary revascularisation), death from coronary heart disease (fatal myocardial infarction or ischaemic heart disease), incident stroke (ischaemic or haemorrhagic events), or death from stroke. A secondary analysis was performed within these selected

**Table 1** Details of studies included in meta-analysis of association of alcohol consumption with selected cardiovascular disease outcomes

Study	Cohort designation	No of subjects	Country	Men (%)	Age range (years)	Study follow-up (years)	Outcomes measured
Albert et al 1999 <sup>22</sup>	Physicians' Health Study	21 537	USA	100	40–84	12	CHD mortality
Bazzano et al 2007 <sup>23</sup>	China National Hypertension Survey Epidemiology Follow-up Study	64 338	China	100	≥40	8	Incident stroke and stroke mortality
Bazzano et al 2009 <sup>24</sup>		64 597	China	100	≥40	8	Incident CHD; CVD and CHD mortality
Berberian et al 1994 <sup>25</sup>	Zoetermeer Cohort	1620	Netherlands	46.9	>20	10	CVD mortality
Berger et al 1999 <sup>26</sup>	Physicians' Health Study	22 071	USA	100	40–84	12.2	Incident stroke
Blackwelder et al 1980 <sup>27</sup>	Honolulu Heart Program	7888	USA	100	Not reported	8	CHD and stroke mortality
Boffetta et al 1990 <sup>28</sup>	American Cancer Society Prospective Study	276 802	USA	100	40–59	12	CHD mortality
Burke et al 2007 <sup>29</sup>	Western Australian Aboriginal cohort	514	Australia	50.2	15–88	11.6	Incident CHD
Camargo et al 1997 <sup>30</sup>	Physicians' Health Study	22 071	USA	100	40–84	11	Incident CHD
Chiuye et al 2008 <sup>31</sup>	Nurses' Health Study	71 243	USA	0	34–59	20	Incident stroke
	Health Professionals Follow-up Study	43 685	USA	100	40–75	18	Incident stroke
Colditz et al 1985 <sup>32</sup>	Massachusetts cohort	1184	USA	38	≥66	4.75	CHD mortality
Cullen et al 1993 <sup>33</sup>	Brusselton, Western Australian cohort	2171	Australia	50	≥40	23	CHD and CVD mortality
Deev et al 1998 <sup>34</sup>	US-Russian Lipid Research Clinics Prevalence Study	4011	USA	46.6	40–69	13	CVD mortality
		4153	Russia	46.7	40–69	13	
Diem et al 2003 <sup>35</sup>	Multinational Study of Vascular Disease in Diabetes	287	Switzerland	56.4	≥35	12.6	CHD mortality
Djousse et al 2002 <sup>36</sup>	Framingham Study	9171	USA	42.2	≥50	10	Incident stroke
Djousse et al 2009 <sup>37</sup>	Women's Health Study	26 399	USA	0	≥45	12	CVD mortality
Doll et al 2005 <sup>38</sup>	British Physician Cohort	12 325	UK	100	48–78	23	CHD mortality
Donahue et al 1986 <sup>39</sup>	Honolulu Heart Program	8006	USA	100	45–69	12	Incident stroke
Ebbert et al 2005 <sup>40</sup>	Iowa Women's Health Study	30 518	USA	0	55–69	14	CHD mortality
	Women's Heart and Health Study	2717	UK	0	60–79	4.7	Incident CHD
Ebrahim et al 2008 <sup>41</sup>	Caerphilly Study	1291	UK	100	47–67	20	
Elkind et al 2006 <sup>42</sup>	Northern Manhattan Study	3176	USA	37.2	≥40	5.9	Incident stroke
Friedman et al 1986 <sup>43</sup>	Framingham Study	4745	USA	44.4	30–59	24	CHD mortality
Fuchs et al 1995 <sup>44</sup>	Nurses' Health Study	85 709	USA	0	34–59	12	CVD mortality
Fuchs et al 2004 <sup>45</sup>	Atherosclerosis Risk in Communities Study	14 506	USA	43.3	45–64	9.8	Incident CHD
Garfinkel et al 1988 <sup>46</sup>	American Cancer Society Prospective Study	581 321	USA	0	>30	12	CHD mortality
Garg et al 1992 <sup>47</sup>	National Health and Nutrition Examination Study	3718	USA	0	45–74	13	CHD mortality
Gaziano et al 2000 <sup>48</sup>	Physicians' Health Study	89 299	USA	100	40–84	5.5	CVD and stroke mortality
Gordon et al 1983 <sup>49</sup>	Framingham Study	4625	USA	43.8	29–62	22	Incident CHD
Gordon et al 1985 <sup>50</sup>	Albany Study	1755	USA	100	38–55	18	Incident CHD
Gronbaek et al 1995 <sup>51</sup>	Copenhagen City Heart Study	13 285	Denmark	45.5	30–79	12	CVD mortality
Gun et al 2006 <sup>52</sup>	Employees of Australian Institute of Petroleum member companies	16 547	Australia	100	NR	20	CHD mortality
Hammar et al 1997 <sup>53</sup>	Swedish Twin Register	1900	Sweden	67.4	30–74	NR	Incident CHD
Hansagi et al 1995 <sup>54</sup>	Swedish Twin Register	15 077	Sweden	47	≥42	20	Stroke mortality
Harriss et al 2007 <sup>55</sup>	Melbourne Collaborative Cohort Study	38 200	Australia	39.7	27–75	11.4	CHD and CVD mortality
Hart et al 2008 <sup>56</sup>	Midspan Collaborative Cohort Study	6000	Scotland	100	35–64	35	CHD and stroke mortality
Hein et al 1996 <sup>57</sup>	Copenhagen Male Study	2826	Denmark	100	53–74	6	Incident CHD
Ikehara et al 2009 <sup>58</sup>	Japan Public Health Center-Based Prospective Study	19 356	Japan	100	40–69	9.9	Incident CHD and stroke
Iso et al 1995 <sup>59</sup>	Rural Japanese cohorts	2890	Japan	100	40–69	10.5	Incident CHD and stroke
Jakovljevic et al 2004 <sup>60</sup>	Institute for Chronic Diseases and Gerontology	286	Serbia and Montenegro	50.7	30–60	20	Stroke mortality
Jamrozik et al 2000 <sup>61</sup>	Perth Community Stroke Study	931	Australia	48	>18	4	CVD mortality
Jousilahti et al 2000 <sup>62</sup>	Finnish Cohort	14 874	Finland	48.2	25–64	12	Incident stroke
Kitamura et al 1998 <sup>63</sup>	Japanese Male Employees	8476	Japan	100	40–59	8.8	Incident CHD
Kittner et al 1983 <sup>64</sup>	Puerto Rico Heart Health Program	9150	Puerto Rico	100	35–79	12	Incident CHD and CHD mortality
Kivela et al 1989 <sup>65</sup>	Two Finnish cohorts from the Seven Countries Study	1112	Finland	100	55–74	10	CVD mortality
Kiyohara et al 1995 <sup>66</sup>	Hisayama Study	1621	Japan	43.6	≥40	26	Incident stroke
Klatsky et al 1990 <sup>67</sup>		123 840	USA	40.5	<30–70	7	CVD mortality
Klatsky et al 1997 <sup>68</sup>	Kaiser Permanente Medical Care Program Cohort	128 934	USA	44	<30–70	NR	Incident CHD
Klatsky et al 2002 <sup>69</sup>		128 934	USA	44	<30–70	18	Incident stroke
Knoops et al 2004 <sup>70</sup>	Healthy Ageing: A Longitudinal Study in Europe	2339	11 European countries	64.4	70–90	10	CHD and CVD mortality

Study	Cohort designation	No of subjects	Country	Men (%)	Age range (years)	Study follow-up (years)	Outcomes measured
Kono et al 1986 <sup>71</sup>	Japanese Male Physician Cohort	5135	Japan	100	NR	19	CHD, CVD and stroke mortality
Leppala et al 1999 <sup>72</sup>	Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort	26 556	Finland	100	50–69	6.1	Incident stroke
Lin et al 2005 <sup>73</sup>	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	110 792	Japan	41.9	40–79	11	CVD mortality
Manttari et al 1997 <sup>74</sup>	Helsinki Heart Study	1924	Finland	100	40–55	5	Incident CHD
Marques-Vidal et al 2004 <sup>75</sup>	PRIME Study—France	7352	France	100	50–59	5	Incident CHD
	PRIME Study—Northern Ireland	2398	Ireland	100	50–59	5	
Maskarinec et al 1998 <sup>76</sup>	Multiethnic cohort (Hawaii)	27 678	USA	50.1	>30	NR	CHD and stroke mortality
Mukamal et al 2003 <sup>77</sup>	Health Professionals Follow-up Study	38 077	USA	100	40–75	12	Incident CHD and CHD mortality
Mukamal et al 2005 <sup>78</sup>	Cardiovascular Health Study	4410	USA	36.1	≥65	9.2	Incident stroke
Mukamal et al 2006 <sup>79</sup>		4410	USA	38.7	≥65	9.2	Incident CHD
Murray et al 2002 <sup>80</sup>	Manitoba Health Cohort	1154	Canada	50.2	18–64	8	Incident CHD
Murray et al 2005 <sup>81</sup>	Lung Health Study	3702	Canada	100	35–60	14	Incident CHD
Pedersen et al 2008 <sup>82</sup>	Copenhagen City Heart Study	11 914	Denmark	44.3	≥20	20	CHD mortality
Rehm et al 1997 <sup>83</sup>	National Health and Nutrition Examination Study	6788	USA	43.6	40–75	14.6	Incident CHD and CHD mortality
Renaud et al 1999 <sup>84</sup>	Cohort from Centre de Medecine Preventive	36 250	France	100	40–60	12–18	CHD and CVD mortality
Salonen et al 1983 <sup>85</sup>	Two counties of eastern Finland	4063	Finland	100	30–59	7	Incident CHD
Sankai et al 2000 <sup>86</sup>	Six Japanese communities	12 372	Japan	40.2	40–69	9.4	Incident stroke
Scherr et al 1992 <sup>87</sup>	Established populations for Epidemiologic Studies of the Elderly	6891	USA	36.9	>65	5	CVD mortality
Shaper et al 1987 <sup>88</sup>	British Regional Heart Study	6103	UK	100	40–59	6.2	Incident CHD
Simons et al 1996 <sup>89</sup>	Dubbo Cohort of New South Wales	2805	Australia	44.1	≥60	6.4	Incident CHD
Solomon et al 2000 <sup>90</sup>	Nurses' Health Study	121 700	USA	0	30–55	NR	Incident CHD and CHD mortality
Suh et al 1992 <sup>91</sup>	Multiple Risk Factor Intervention Trial	11 688	USA	100	35–57	3.8	CHD mortality
Suhonen et al 1987 <sup>92</sup>	Social Insurance Institution's Mobile Clinic Health Survey	4532	Finland	100	40–64	5	CHD mortality
Thun et al 1997 <sup>93</sup>	Cancer Prevention Study II	489 626	USA	51.3	30–104	9	CHD, CVD and stroke mortality
Tolstrup et al 2006 <sup>94</sup>	Danish Cohort	53 500	Denmark	46.8	50–65	5.7	Incident CHD
Trevisan et al 2001 <sup>95</sup>	Risk Factors and Life Expectancy Study	8647	Italy	100	30–59	7	CHD and CVD mortality
Truelsen et al 1998 <sup>96</sup>	Copenhagen City Heart Study	13 329	Denmark	45.5	45–84	16	Incident stroke
Valmadril et al 1999 <sup>97</sup>	Wisconsin Epidemiologic Study of Diabetic Retinopathy	983	USA	45.2	NR	12.3	CHD mortality
Waskiewicz et al 2004 <sup>98</sup>	Pol-MONICA Programme	5452	Poland	49.3	35–64	NR	CVD mortality
Wellmann et al 2004 <sup>99</sup>	MONICA Augsburg Cohort	2710	Germany	49.6	35–64	10	Incident CHD
Wilkins 2002 <sup>100</sup>	National Population Health Survey	6014	Canada	43.8	≥40	4	Incident CHD
Woo et al 1990 <sup>101</sup>	Elderly Chinese Cohort	427	China	40	≥60	2.5	Incident stroke
Xu et al 2007 <sup>102</sup>	Husbands from Shanghai Women's Health Study	64 515	China	100	30–89	4.6	CHD and CVD mortality
Yang et al 1999 <sup>103</sup>	South Bay Heart Watch Cohort	1196	USA	89	≥45	3.4	Incident CHD
Yuan et al 1997 <sup>104</sup>	Four communities in Shanghai	18 244	China	100	45–64	6.7	CHD and stroke mortality
Zhang et al 2004 <sup>105</sup>	Northern and southern Chinese populations	12 352	China	100	35–59	15.2	Incident stroke

CHD=coronary heart disease. CVD=cardiovascular disease.

studies to determine the association between alcohol consumption and the risk of death from all causes.

Both reviewers independently extracted data from all studies fulfilling the inclusion criteria, and any disagreement was resolved by consensus. We extracted the data elements of cohort name, sample size, and population demographics (country, percentage male, mean age or age range). We also extracted information for key indicators of study quality in observational studies proposed by Egger et al<sup>10</sup> and Laupacis et al.<sup>12</sup> Specifically, we evaluated the effect on each outcome of the number of potential confounding variables and the number of years participants were followed.

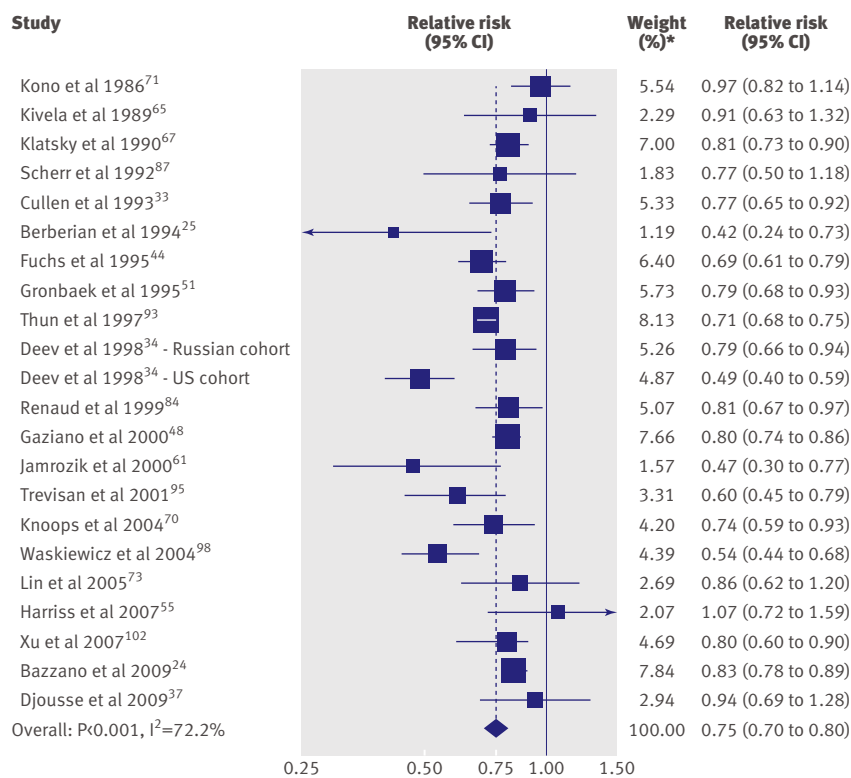
#### Data synthesis and analysis

The relative risk was used as the common measure of association across studies. Hazard ratios and incidence density ratios were directly considered as relative risks. Where necessary, odds ratios were transformed into relative risks with this formula:

Relative risk=odds ratio/[(1-P<sub>o</sub>)+(P<sub>o</sub>×odds ratio)], in which P<sub>o</sub> is the incidence of the outcome of interest in the non-exposed group.<sup>13</sup>

The standard error of the resulting converted relative risk was then determined with this formula:

SElog(relative risk)=SElog(odds ratio)×log(relative risk)/log(odds ratio).



\*Weight from random effects analysis

**Fig 2** | Forest plot of mortality from cardiovascular disease associated with alcohol consumption

Because these transformations can underestimate the variance of the relative risks derived from the odds ratios,<sup>14,15</sup> we performed a sensitivity analysis that excluded four studies for which this transformation had been applied. All analyses were performed with Stata 10.0 (StataCorp, College Station TX, USA). The Stata “metan” command was used to pool the  $\ln(\text{relative risks})$  across studies according to the DerSimonian and Laird random effects model.<sup>16</sup>

In some studies, a single relative risk (or odds ratio) was not available for drinkers versus non-drinkers because the data were presented as only a dose-response (that is, several alcohol consumption levels relative to non-drinkers). In these cases, we first pooled across levels of intake within the study using a random effects model to derive a single relative risk for drinkers versus non-drinkers. The resulting single, study-specific relative risk was then pooled with those of other studies.

To visually assess the relative risk estimates and corresponding 95% confidence intervals across studies, we generated forest plots sorted by year of publication. Analyses were stratified by study quality criteria and by participant characteristics.

To assess heterogeneity of relative risks across studies, we inspected forest plots and calculated  $Q$  (significance level of  $P \leq 0.10$ ) and  $I^2$  statistics.<sup>17,18</sup> In the presence of heterogeneity, random effects models were used (rather than fixed effects models) to obtain pooled effect estimates across studies. Sensitivity

analyses and stratified analyses were performed to assess the associations of selected study quality and clinical factors on cardiovascular risk, including number of confounding factors and duration of follow-up dichotomised at the median value. We also performed a sensitivity analysis excluding studies reporting only odds ratios. We conducted a cumulative meta-analysis of studies ordered chronologically to assess the sequential contributions of studies published over time.<sup>19</sup> Finally, we assessed evidence of publication bias through visual inspection of funnel plots and Begg’s rank correlation test for asymmetry.<sup>20,21</sup>

## RESULTS

### Identification of studies

Our initial search yielded a total of 4235 unique citations (fig 1). After two rounds of reviews and searching citations of retained articles, we identified 131 studies as potentially relevant for analysis. We excluded studies of cardiovascular outcomes predefined as ineligible (such as chronic congestive heart failure or stable angina), non-atherothrombotic end points (such as arrhythmias), composite end points, or non-cardiovascular outcomes (such as cancer), and duplicate reports. This left 84 studies for our systematic review and meta-analysis. Table 1 provides details of the included studies.<sup>22–105</sup> Of these 84 studies, 34 (40%) reported on all-male cohorts, six (7%) reported on women only, and 44 (52%) included both men and women.

### Study quality

We evaluated two primary features of study quality—the number of years that participants were followed and adjustment for confounding. Duration of follow-up for study end points ranged from 2.5 to 35 years, with a mean follow-up of 11 years (standard deviation 6 years) (table 1). Of the included studies, 13 (15%) had  $\leq 5$  years of follow-up. Similarly, studies varied in the degree of confounder adjustment, ranging from none to 18 variables, with a mean of six (SD 4). Most studies (68) presented adjusted estimates, but eight reported only unadjusted estimates and another eight adjusted only for basic demographic information. Methods of adjustment, effect measure, and confounding variables used in each study are presented in the appendix tables 1–5 on [bmj.com](http://www.bmj.com) for each of our primary outcomes.

### Primary analyses of cardiovascular disease mortality, coronary heart disease incidence and mortality, and stroke incidence and mortality

For cardiovascular disease mortality and both end points for coronary heart disease, alcohol consumption was associated with lower risk, with relative risks of about 0.75 (table 2). In general, relative risks derived from the more highly adjusted and from the less adjusted results were similar. Figures 2–4 reveal little visual evidence of heterogeneity despite statistical evidence of heterogeneity ( $P < 0.001$ ,  $I^2 = 72.2\%$ ), probably driven by the large number of participants ( $> 1$

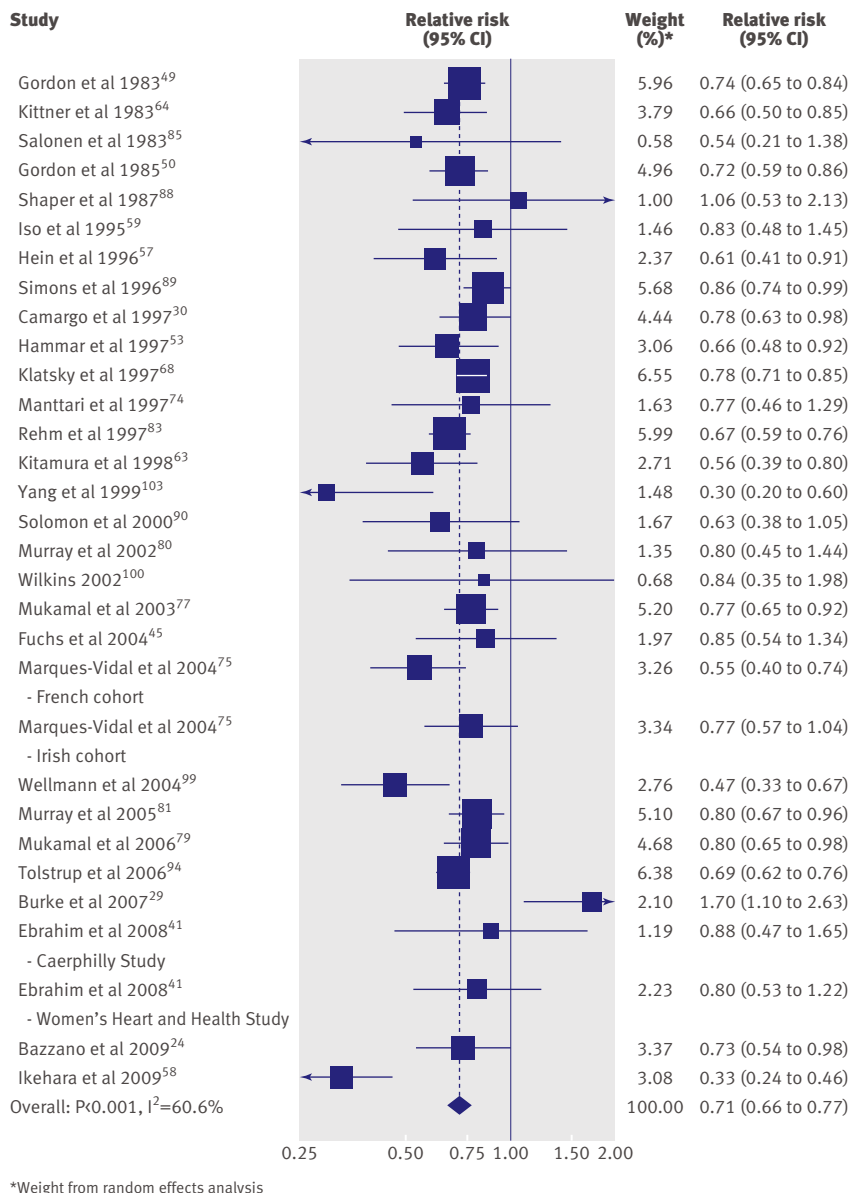


Fig 3 | Forest plot of incident coronary heart disease associated with alcohol consumption

million). All the point estimates were <math>< 1.0</math> in studies, except for one study for cardiovascular disease mortality and two studies for coronary heart disease incidence and mortality.

In contrast, the overall associations of alcohol intake with stroke incidence and mortality were close to null, both in minimally adjusted and more highly adjusted models (table 2, figs 5 and 6). However, this null association seemed to obscure nearly significant but opposite associations with subtypes of incident stroke. Among the 12 studies on incident haemorrhagic stroke, the pooled relative risk for current alcohol drinkers compared with non-drinkers was 1.14 (95% confidence interval 0.97 to 1.34), whereas the eight studies on ischaemic stroke showed a moderate reduction in the pooled relative risk of 0.92 (0.85 to 1.00). Alcohol use was not associated with stroke mortality, but few studies assessed the risk of mortality from

haemorrhagic or ischaemic stroke separately. Furthermore, only two studies reported relative risks on stroke end points for former drinkers compared with non-drinkers.

Analyses of dose response

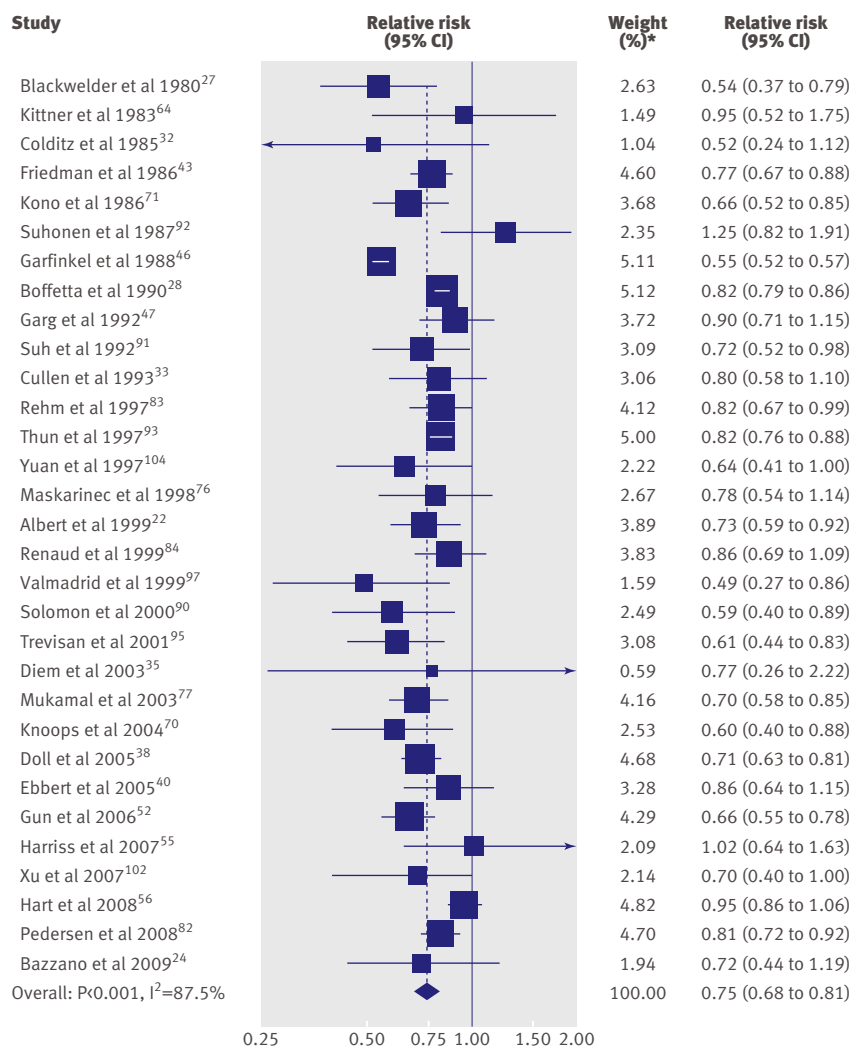
Analyses of the dose of alcohol consumed showed that 2.5–14.9 g alcohol (about  $\leq 1$  drink) per day was protective for all five outcomes compared with no alcohol (table 2). For coronary heart disease outcomes, all levels of intake >2.5 g/day had similar degrees of risk reduction. For cardiovascular disease mortality as well as stroke incidence and mortality, the dose-response relations were less clear and more consistent with U or J shaped curves, suggesting an increased risk among drinkers of greater amounts of alcohol. Specifically, those who consumed >60 g/day were at a significantly increased risk of incident stroke compared with abstainers (relative risk 1.62 (1.32 to 1.98)).

Sensitivity analyses

In an analysis of differences in associations by sex, any amount of alcohol consumption relative to none was associated with greater reduction in cardiovascular disease mortality, stroke incidence, and stroke mortality for women than men. However, the association with stroke should be interpreted with caution, as the risk estimates for women are based on only three pooled studies. On the other hand, similar associations by sex were observed for coronary heart disease incidence and mortality (table 2).

Sensitivity analyses that were confined to only studies that controlled for the important confounders of smoking, age, and sex revealed generally similar results for all of the outcomes. Additional sensitivity analyses that account for the median number of confounding variables in the multivariable analyses of included studies revealed that those with fewer (less than the median) confounding variables generally reported slightly lower relative risk estimates. However, this pattern was inconsistent across the outcomes. Specifically, an increased risk of stroke mortality was observed for studies with limited adjustment for confounding. A similar trend was observed when considering the duration of follow-up. Using the pooled median number of years as the cut point, we found that studies with shorter follow-up reported a greater risk reduction for all outcomes except cardiovascular disease and coronary heart disease mortality (table 2).

Among those studies that used long term abstainers as the referent category, excluding former drinkers or evaluating them separately, the estimated association between drinking and both incidence and mortality estimates did not change substantively (table 2). Among studies that evaluated former drinkers separately, the risk of death (from cardiovascular disease and coronary heart disease) was significantly higher in former drinkers than in drinkers. However, former drinkers did not have an increased risk of incident cardiovascular events (coronary heart disease or stroke).



<sup>\*</sup>Weight from random effects analysis

**Fig 4** | Forest plot of mortality from coronary heart disease associated with alcohol consumption

Finally, a sensitivity analysis that excluded the few studies where only odds ratios instead of relative risks were presented had little effect on the results. In cumulative meta-analyses of cardiovascular disease and coronary heart disease outcomes (appendix figs 1–3 on [bmj.com](http://bmj.com)), there was little variation in the relative risk associated with alcohol consumption on cardiovascular disease mortality or incident coronary heart disease with addition of new studies after 1999; for coronary heart disease mortality, this plateau in incremental change from new studies occurred as early as 1992–3.

#### Mortality from all causes

Of the 84 studies addressing alcohol and cardiovascular disease events, 31 also examined the association of alcohol consumption with all cause mortality. The pooled estimates from these studies showed a lower risk of all cause mortality for drinkers compared with non-drinkers (relative risk 0.87 (0.83 to 0.92)) (fig 7). However, the association was J shaped, with the lowest risk for those consuming 2.5–14.9 g/day

(relative risk 0.83 (0.80 to 0.86), 16 studies) and an elevated risk in those consuming >60 g/day (relative risk 1.30 (1.22 to 1.38), 8 studies).

#### Publication bias

Visual inspection of the funnel plot for each outcome did not show asymmetry, an indication that significant publication bias was not likely. This was further confirmed by a non-significant Begg's test for each outcome (for cardiovascular disease mortality,  $P=0.40$ ; incident coronary heart disease,  $P=0.75$ ; coronary heart disease mortality,  $P=0.089$ ; incident stroke,  $P=0.33$ ; stroke mortality,  $P=0.59$ ; all cause mortality,  $P=0.26$ ).

#### DISCUSSION

In this review of 84 studies of alcohol consumption and cardiovascular disease, alcohol consumption at 2.5–14.9 g/day (about  $\leq 1$  drink a day) was consistently associated with a 14–25% reduction in the risk of all outcomes assessed compared with abstaining from alcohol. Such a reduction in risk is potentially of clinical importance, but consumption of larger amounts of alcohol was associated with higher risks for stroke incidence and mortality.

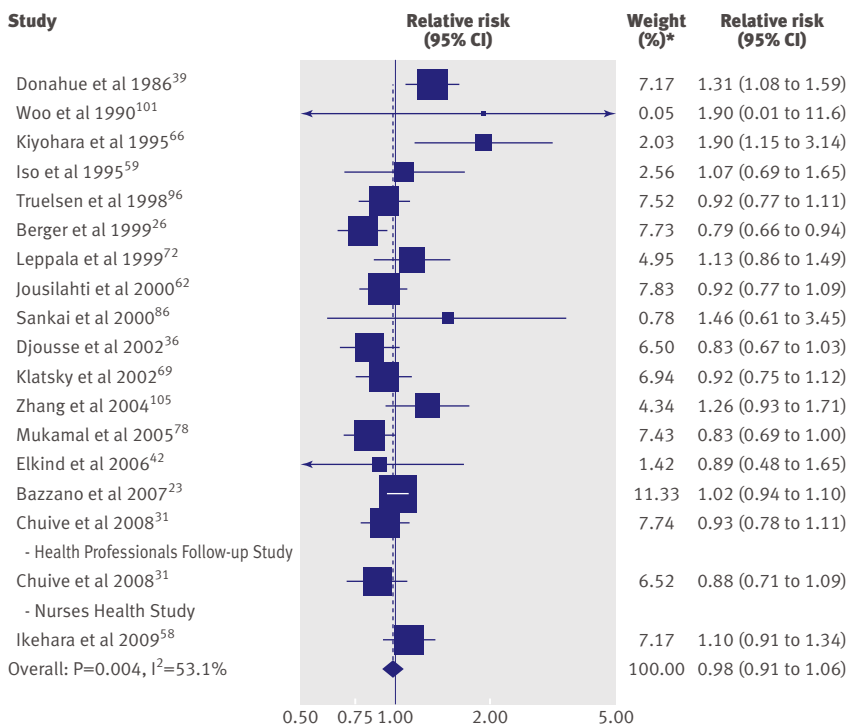
To our knowledge, this systematic review and meta-analysis is the most comprehensive to date. Although roughly similar estimates of lower risk were observed in previous meta-analyses of both coronary heart disease and stroke,<sup>1–8</sup> our review extends the findings by assessing a broader array of relevant cardiovascular outcomes and adding several new important studies. Our review clarifies several discrepancies among prior reports. Corrao et al reported a J shaped relation between alcohol intake and coronary heart disease,<sup>2</sup> whereas the review by Maclure described this relation as L shaped because he did not observe an increase in coronary heart disease risk associated with higher alcohol consumption.<sup>6</sup> Our updated meta-analysis supports the latter association for coronary heart disease, with a 25–35% risk reduction for light to moderate drinking<sup>106</sup> that also is present with heavier drinking.

Our analysis of multiple cardiovascular outcomes also shows the complexities inherent in the study of alcohol consumption. Modest alcohol intake was associated with lower stroke incidence and mortality, but the risk increased substantially with heavier drinking (that is, a J shaped relation). Furthermore, the association of alcohol consumption is complex and differs by stroke subtype, with a slightly lower risk of ischaemic stroke but higher risk of haemorrhagic stroke. These differential associations probably reflect the known antithrombotic effects of alcohol.<sup>107</sup> Alcohol consumption, particularly at high doses, also seems to have an adverse association with blood pressure that may account, in part, for the higher risk of haemorrhagic stroke associated with heavier drinking.<sup>108</sup> Additionally, our analysis does not consider other known detrimental effects of high alcohol consumption.<sup>3</sup> Therefore, our findings lend further support for limits on alcohol consumption.<sup>106 109</sup>

**Table 2** | Stratified analyses of pooled relative risks (95% CI) for cardiovascular and stroke outcomes (number of pooled studies in parentheses after each effect estimate)

	Cardiovascular disease mortality (n=21 studies, 1 184 956 subjects)	Coronary heart disease		Stroke	
		Incident (n=29 studies, 549 504 subjects)	Mortality (n=31 studies, 1 925 106 subjects)	Incident (n=17 studies, 458 811 subjects)	Mortality (n=10 studies, 723 571 subjects)
<b>Active drinkers v non-drinkers:</b>					
Least adjusted models	0.84 (0.75 to 0.95) (11)	0.73 (0.65 to 0.82) (14)	0.80 (0.70 to 0.91) (10)	1.01 (0.88 to 1.16) (10)	1.13 (0.96 to 1.32) (3)
Most adjusted models	0.75 (0.70 to 0.80) (21)	0.71 (0.66 to 0.77) (29)	0.75 (0.68 to 0.81) (31)	0.98 (0.91 to 1.06) (17)	1.06 (0.91 to 1.23) (10)
<b>Active drinkers v lifetime abstainers</b>					
Former drinkers v non-drinkers	1.48 (1.23 to 1.79) (6)	1.10 (0.91 to 1.33) (8)	1.31 (1.02 to 1.68) (6)	0.87 (0.72 to 1.07) (4)	Not reported (2)
<b>Alcohol intake (g/day) v none:</b>					
<2.5	0.71 (0.57 to 0.89) (7)	0.96 (0.86 to 1.06) (6)	0.92 (0.80 to 1.06) (6)	0.81 (0.74 to 0.89) (3)	1.00 (0.75 to 1.34) (3)
2.5–14.9	0.77 (0.71 to 0.83) (15)	0.75 (0.65 to 0.88) (9)	0.79 (0.73 to 0.86) (18)	0.80 (0.74 to 0.87) (3)	0.86 (0.75 to 0.99) (6)
15–29.9	0.75 (0.70 to 0.80) (13)	0.66 (0.59 to 0.75) (15)	0.79 (0.71 to 0.88) (15)	0.92 (0.82 to 1.04) (5)	1.15 (0.86 to 1.54) (6)
30–60	0.85 (0.73 to 0.98) (10)	0.67 (0.56 to 0.79) (9)	0.77 (0.72 to 0.83) (12)	1.15 (0.98 to 1.35) (4)	1.10 (0.85 to 1.45) (5)
>60	0.99 (0.84 to 1.17) (6)	0.76 (0.52 to 1.09) (9)	0.75 (0.63 to 0.89) (9)	1.62 (1.32 to 1.98) (4)	1.44 (0.99 to 2.10) (3)
<b>Sex:</b>					
Men	0.80 (0.73 to 0.87) (13)	0.71 (0.66 to 0.77) (25)	0.77 (0.72 to 0.82) (21)	1.02 (0.92 to 1.13) (11)	1.07 (0.89 to 1.28) (9)
Women	0.69 (0.60 to 0.78) (9)	0.71 (0.66 to 0.77) (11)	0.78 (0.64 to 0.94) (10)	0.87 (0.75 to 1.01) (4)	0.81 (0.67 to 0.98) (3)
<b>Adjustment for confounding factors*:</b>					
Weak	0.74 (0.67 to 0.82) (10)	0.69 (0.62 to 0.76) (11)	0.72 (0.63 to 0.83) (15)	0.99 (0.86 to 1.13) (7)	1.30 (1.11 to 1.52) (5)
Strong	0.76 (0.70 to 0.83) (11)	0.72 (0.65 to 0.79) (18)	0.80 (0.75 to 0.86) (16)	0.99 (0.89 to 1.09) (10)	0.96 (0.81 to 1.14) (5)
<b>Median follow-up time†:</b>					
Short	0.76 (0.71 to 0.83) (8)	0.71 (0.65 to 0.79) (14)	0.75 (0.67 to 0.85) (12)	0.98 (0.90 to 1.07) (9)	1.01 (0.82 to 1.24) (5)
Long	0.75 (0.67 to 0.84) (13)	0.72 (0.64 to 0.80) (15)	0.75 (0.67 to 0.84) (19)	1.00 (0.88 to 1.13) (8)	1.18 (1.02 to 1.37) (5)

\*Adjustment for confounding factors was dichotomised as weak (median value) or strong (≥median value). Cut points: ≥5 for coronary heart disease and stroke mortality, ≥6 for cardiovascular disease mortality and incident coronary heart disease, ≥7 for incident stroke.  
 †Total follow-up time was dichotomised as short (<median value) or long (≥median value). Cut points: ≥9 for incident coronary heart disease, ≥10 for cardiovascular disease mortality, ≥12 for coronary heart disease mortality and incident stroke, ≥14 for stroke mortality.



\*Weight from random effects analysis

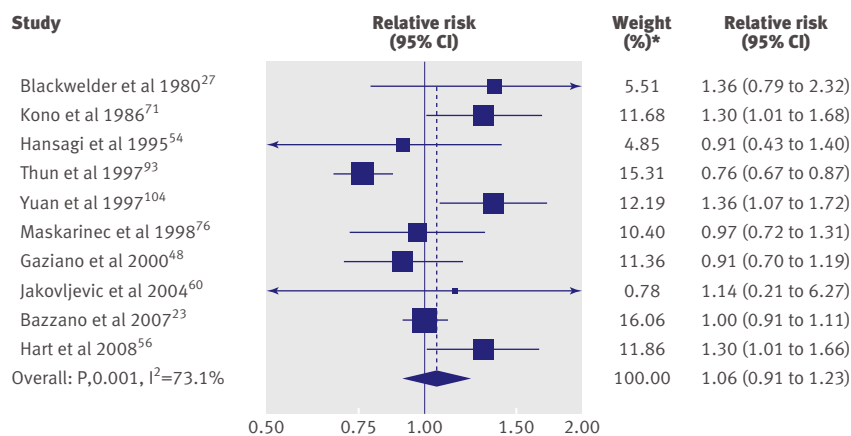
**Fig 5** | Forest plot of incident stroke associated with alcohol consumption

Our review also highlights other important aspects of the relation between alcohol consumption and cardiovascular disease. Firstly, the lower risk of coronary heart disease associated with alcohol consumption was at least as strong for women as for men. Limited evidence suggests that the risk of stroke related to alcohol is lower for women than men, but this may only reflect lower alcohol intake among women. Secondly, inclusion of former drinkers did not seem to bias the association of alcohol consumption with cardiovascular disease. Thirdly, when studies were summarised chronologically, we found that the overall association between drinking and cardiovascular disease and coronary heart disease became apparent at least a decade ago, and ongoing studies have done little to revise the estimated associations.

**An argument for causation**

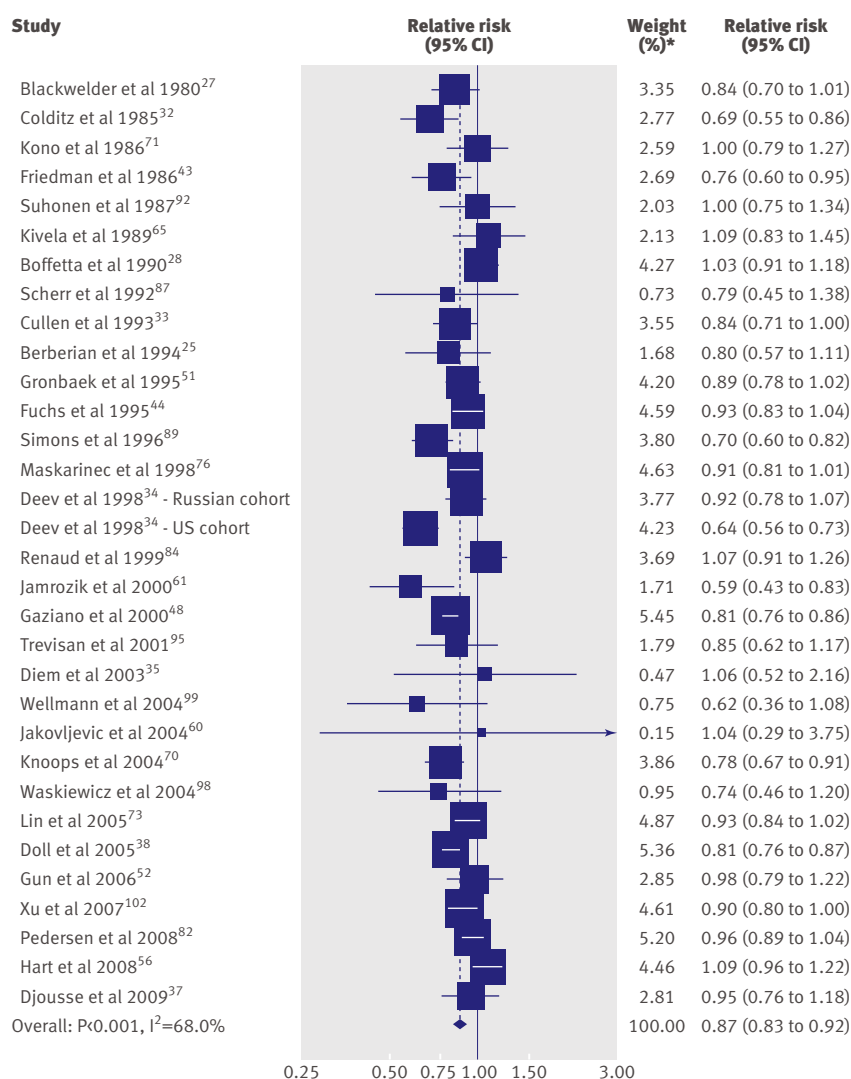
From the extensive body of literature summarised here, the association between alcohol consumption and decreased cardiovascular risk is not in question, as additional research has not changed this conclusion. Rather, the lingering question is whether this association is causal. Clearly, observational studies cannot establish causation. However, when the present results are coupled with those from our companion review paper summarising interventional mechanistic studies





\*Weight from random effects analysis

Fig 6 | Forest plot of mortality from stroke associated with alcohol consumption



\*Weight from random effects analysis

Fig 7 | Forest plot of mortality from all causes associated with alcohol consumption

focusing on biomarkers associated with cardiovascular disease,<sup>110</sup> the argument for causation becomes more compelling. Indeed, the mechanistic biomarker review shows biological plausibility for a causal association by showing favourable changes in pathophysiologically relevant molecules.

Therefore, we can now examine the argument for causation based on Hill's criteria.<sup>111</sup> Beyond the biological plausibility argument discussed above, there is an appropriate temporal relation with alcohol use preventing cardiovascular disease. Secondly, we have observed a greater protective association with increasing dose, except that it seems to be offset somewhat by negative associations with the risk of haemorrhagic stroke. Thirdly, the protective association of alcohol has been consistently observed in diverse patient populations and in both women and men. Fourthly, the association is specific: moderate drinking (up to 1 drink or 12.5 g alcohol per day for women and 2 drinks or 25 g alcohol per day for men<sup>106</sup>) is associated with lower rates of cardiovascular disease but is not uniformly protective for other conditions, such as cancer.<sup>112</sup> Lastly, the reduction in risk is notable even when controlling for known confounders (such as smoking, diet, and exercise). Any potential unmeasured confounder would need to be very strong to explain away the apparently protective association.

#### Limitations of study

The results of our meta-analysis should be interpreted in context of the limitations of available data. Firstly, the quality of individual studies varied, with some studies having limited follow-up and limited adjustment for potential confounding. With respect to study follow-up, it is possible that misclassification of alcohol consumption may increase with study length because of changes in drinking habits over time. It is also possible that potential biological effects of alcohol vary with time of exposure. However, arguing against both these possibilities, the analysis stratified by length of follow-up did not show different associations between alcohol intake and outcome for shorter follow-up times versus longer times.

Secondly, only a limited subset of studies provided specific risk estimates for different beverages. Although there is great interest in differences between beer, wine, and spirits, alcoholic drinks generally have similar effects on high density lipoprotein cholesterol,<sup>113</sup> and it is likely that any particular benefit of wine is prone to confounding by diet and socioeconomic status.<sup>114,115</sup> None the less, this remains an interesting topic for further investigation.

Thirdly, we found only limited information on the relation between alcohol intake and mortality from subtypes of stroke, so this topic continues to be important for large observational cohort studies. Finally, we observed significant heterogeneity across studies for several of our pooled analyses. This may be due in great part to large study sample sizes, which can confer greater statistical power to heterogeneity tests, whereas the clinical relevance of this heterogeneity may be

**WHAT IS ALREADY KNOWN ON THIS TOPIC:**

Systematic reviews have addressed the association of alcohol consumption with various cardiovascular outcomes

However, these reviews are somewhat out of date, and none has comprehensively studied a broad spectrum of relevant cardiovascular end points

**WHAT THIS STUDY ADDS**

This meta-analysis provides a summary of current knowledge regarding alcohol associations with six meaningful clinical end points—cardiovascular disease mortality, coronary heart disease incidence and mortality, stroke incidence and mortality, and all cause mortality

The results confirm the beneficial effects of moderate alcohol consumption and the need to elucidate the underlying pathophysiological mechanisms

quite modest.<sup>10</sup> Visual inspection of our various forest plots and the relative consistency of pooled relative risks across clinical and methodological variables suggest that there is considerable consistency in the relative risk findings across studies and across strata.

**Implications**

Given the consistency observed in our findings and compelling mechanistic data pointing to causation in our companion review, additional observational studies will have limited value except to elucidate more precisely the association of alcohol and stroke.<sup>116</sup> Rather, debate should centre now on how to integrate this evidence into clinical practice and public health messages. In the realm of clinical practice, the evidence could form a foundation for proposing counselling for selected patients to incorporate moderate amounts of alcohol into their diets to improve their coronary heart disease risk. However, such a clinical strategy requires formal evaluation in pragmatic clinical trials that assess the questions of optimal patient selection, compliance, risks, and benefits. The focus of such trials would shift from assessing the association between alcohol and disease outcomes to evaluating the receptivity of both physicians and patients to the recommended consumption of alcohol for therapeutic purposes and the extent to which it can be successfully and safely implemented. In support of implementation trials, our two papers show that alcohol consumption in moderation has reproducible and plausible effects on markers of coronary heart disease risk.

With respect to public health messages, there may now be an impetus to better communicate to the public that alcohol, in moderation, may have overall health benefits that outweigh the risks in selected subsets of patients. Again, any such strategy would need to be accompanied by rigorous study and oversight of impacts. One approach would be to undertake public health messaging pilot studies on well defined target populations (such as a workplace or in a small jurisdiction) to permit detailed evaluation of effects on measures such as knowledge, attitudes, self reported drinking behaviours, and perhaps, secondarily, health outcomes.

The debate on how to integrate this evidence into clinical practice and public health messages will require integration of all possible effects of alcohol—from injury and violence to glucose metabolism and inflammation—and recognition that these effects may be distributed unequally across the population. For example, injury risk probably disproportionately affects younger individuals, whereas cardiovascular disease mainly affects older adults. Robust studies that examine multiple outcomes simultaneously are needed to identify those subsets of the population in which reduced cardiovascular risk might dominate against those for whom the risks of social and medical problems (including several cancers and injury<sup>112 117</sup>) are too great. Despite the latter concerns, results of our secondary analysis of overall mortality (fig 5) support the notion that moderate alcohol consumption is associated with net benefit, at least in populations similar to those studied in the extant literature.

Our two systematic review papers summarise a surprisingly extensive body of literature on the relation between alcohol and cardiovascular disease. Our findings point to the need to define implications for clinical and public health practice. These reviews and the perspectives above provide a foundation for that dialogue.

Preliminary results from this manuscript were presented at the 32nd annual meeting of the Society of General Internal Medicine, Miami, Florida, 14 May 2009.

**Contributors:** All authors conceived the study and developed the protocol. PER and SEB conducted the search, abstracted the data for the analysis, and performed the statistical analysis. PER, SEB, and WAG wrote the first draft of the manuscript. All authors had access to the data, critically reviewed the manuscript for important intellectual content, and approved the final version of the manuscript. WAG will act as guarantor for the paper.

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**Competing interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: support from the Robert Wood Johnson Foundation, the Substance Abuse and Mental Health Services, and the Administration Center for Substance Abuse Treatment (as detailed above) for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** Not required.

**Data sharing:** Statistical code and datasets available from the corresponding author at [wghali@ucalgary.ca](mailto:wghali@ucalgary.ca)

- 1 Cleophas TJ. Wine, beer and spirits and the risk of myocardial infarction: a systematic review. *Biomed Pharmacother* 1999;53:417-23.
- 2 Corrao G, Rubbiati L, Bagnardi V, Zamboni A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. *Addiction* 2000;95:1505-23.

- 3 Corrao G, Bagnardi V, Zamboni A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004;38:613-9.
- 4 Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* 2002;105:2836-44.
- 5 Fillmore KM, Kerr WC, Stockwell T, Chikritzts T, Bostrom A. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. *Addiction Res Theory* 2006;14:101-32.
- 6 Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev* 1993;15:328-51.
- 7 Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA* 2003;289:579-88.
- 8 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ* 1996;312:731-6.
- 9 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
- 10 Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. BMJ Publishing Group, 2001.
- 11 Turner C. How much alcohol is in a "standard drink"? An analysis of 125 studies. *Br J Addict* 1990;85:1171-5.
- 12 Laupacis A, Wells G, Richardson S, Tugwell P. Users' guides to the medical literature: how to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994;272:234-7.
- 13 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-1.
- 14 Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol* 2004;160:301-5.
- 15 McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003;157:940-3.
- 16 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- 17 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
- 18 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 19 Muellerleile P, Mullen B. Sufficiency and stability of evidence for public health interventions using cumulative meta-analysis. *Am J Public Health* 2006;96:515-22.
- 20 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
- 21 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.
- 22 Albert CM, Manson JE, Cook NR, Ajani UA, Gaziano JM, Hennekens CH. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation* 1999;100:944-50.
- 23 Bazzano LA, Gu D, Reynolds K, Wu X, Chen CS, Duan X, et al. Alcohol consumption and risk for stroke among Chinese men. *Ann Neurol* 2007;62:569-78.
- 24 Bazzano LA, Gu D, Reynolds K, Chen J, Wu X, Chen CS, et al. Alcohol consumption and risk of coronary heart disease among Chinese men. *Int J Cardiol* 2009;135:78-85.
- 25 Berberian KM, van Duijn CM, Hoes AW, Valkenburg HA, Hofman A. Alcohol and mortality. Results from the EPOZ (Epidemiologic Study of Cardiovascular Risk Indicators) follow-up study. *Eur J Epidemiol* 1994;10:587-93.
- 26 Berger K, Ajani UA, Kase CS, Gaziano JM, Buring JE, Glynn RJ, et al. Light-to-moderate alcohol consumption and risk of stroke among US male physicians. *N Engl J Med* 1999;341:1557-64.
- 27 Blackwelder WC, Yano K, Rhoads GG, Kagan A, Gordon T, Palesch Y. Alcohol and mortality: the Honolulu Heart Study. *Am J Med* 1980;68:164-9.
- 28 Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology* 1990;1:342-8.
- 29 Burke V, Lee AH, Hunter E, Spargo R, Smith R, Beilin LJ, et al. Alcohol intake and incidence of coronary disease in Australian aborigines. *Alcohol* 2007;42:119-24.
- 30 Camargo CA, Hennekens CH, Gaziano JM, Glynn RJ, Manson JE, Stampfer MJ. Prospective study of moderate alcohol consumption and mortality in US male physicians. *Arch Intern Med* 1997;157:79-85.
- 31 Chiave SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation* 2008;118:947-54.
- 32 Colditz GA, Branch LG, Lipnick RJ, Willett WC, Rosner B, Posner B, et al. Moderate alcohol and decreased cardiovascular mortality in an elderly cohort. *Am Heart J* 1985;109:886-9.
- 33 Cullen KJ, Knuiman MW, Ward NJ. Alcohol and mortality in Busselton, Western Australia. *Am J Epidemiol* 1993;137:242-8.
- 34 Deev A, Shestov D, Abernathy J, Kapustina A, Muhina N, Irving S. Association of alcohol consumption to mortality in middle-aged US and Russian men and women. *Ann Epidemiol* 1998;8:147-53.
- 35 Diem P, Deplazes M, Fajfr R, Bearth A, Muller B, Christ ER, et al. Effects of alcohol consumption on mortality in patients with type 2 diabetes mellitus. *Diabetologia* 2003;46:1581-5.
- 36 Djousse L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke: the Framingham Study. *Stroke* 2002;33:907-12.
- 37 Djousse L, Lee IM, Buring JE, Gaziano JM. Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms. *Circulation* 2009;120:237-44.
- 38 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to alcohol consumption: a prospective study among male British doctors. *Int J Epidemiol* 2005;34:199-204.
- 39 Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke. The Honolulu Heart Program. *JAMA* 1986;255:2311-4.
- 40 Ebbert JO, Janney CA, Sellers TA, Folsom AR, Cerhan JR. The association of alcohol consumption with coronary heart disease mortality and cancer incidence varies by smoking history. *J Gen Intern Med* 2005;20:14-20.
- 41 Ebrahim S, Lawlor DA, Shlomo YB, Timpson N, Harbord R, Christensen M, et al. Alcohol dehydrogenase type 1C (ADH1C) variants, alcohol consumption traits, HDL-cholesterol and risk of coronary heart disease in women and men: British Women's Heart and Health Study and Caerphilly cohorts. *Atherosclerosis* 2008;196:871-8.
- 42 Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 2006;37:13-9.
- 43 Friedman LA, Kimball AW. Coronary heart disease mortality and alcohol consumption in Framingham. *Am J Epidemiol* 1986;124:481-9.
- 44 Fuchs CS, Stampfer MJ, Colditz GA, Giovannucci EL, Manson JE, Kawachi I, et al. Alcohol consumption and mortality among women. *N Engl J Med* 1995;332:1245-50.
- 45 Fuchs FD, Chambless LE, Folsom AR, Eigenbrodt ML, Duncan BB, Gilbert A, et al. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2004;160:466-74.
- 46 Garfinkel L, Boffetta P, Stellman SD. Alcohol and breast cancer: a cohort study. *Prev Med* 1988;17:686-93.
- 47 Garg R, Wagener DK, Madans JH. Alcohol consumption and risk of ischemic heart disease in women. *Arch Intern Med* 1993;153:1211-6.
- 48 Gaziano JM, Gaziano TA, Glynn RJ, Sesso HD, Ajani UA, Stampfer MJ, et al. Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *J Am Coll Cardiol* 2000;35:96-105.
- 49 Gordon T, Kannel WB. Drinking habits and cardiovascular disease: the Framingham Study. *Am Heart J* 1983;105:667-73.
- 50 Gordon T, Doyle JT. Drinking and coronary heart disease: the Albany Study. *Am Heart J* 1985;110:331-4.
- 51 Gronbaek M, Deis A, Sorensen TI, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine, beer, or spirits. *BMJ* 1995;310:1165-9.
- 52 Gun RT, Pratt N, Ryan P, Gordon I, Roder D. Tobacco and alcohol-related mortality in men: estimates from the Australian cohort of petroleum industry workers. *Aust N Z J Public Health* 2006;30:318-24.
- 53 Hammar N, Romelsjo A, Alfredsson L. Alcohol consumption, drinking pattern and acute myocardial infarction. A case referent study based on the Swedish Twin Register. *J Intern Med* 1997;241:125-31.
- 54 Hansagi H, Romelsjo A, Gerhardsson de Verdier M, Andreasson S, Leifman A. Alcohol consumption and stroke mortality. 20-year follow-up of 15,077 men and women. *Stroke* 1995;26:1768-73.
- 55 Harriss LR, English DR, Hopper JL, Powles J, Simpson JA, O'Dea K, et al. Alcohol consumption and cardiovascular mortality accounting for possible misclassification of intake: 11-year follow-up of the Melbourne Collaborative Cohort Study. *Addiction* 2007;102:1574-85.
- 56 Hart CL, Smith GD. Alcohol consumption and mortality and hospital admissions in men from the Midspan Collaborative cohort study. *Addiction* 2008;103:1979-86.
- 57 Hein HO, Suadicani P, Gyntelberg F. Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow up in the Copenhagen male study. *BMJ* 1996;312:736-41.

- 58 Ikehara S, Iso H, Yamagishi K, Yamamoto S, Inoue M, Tsugane S, et al. Alcohol consumption, social support, and risk of stroke and coronary heart disease among Japanese men: the JPHC Study. *Alcohol Clin Exp Res* 2009;33:1025-32.
- 59 Iso H, Kitamura A, Shimamoto T, Sankai T, Naito Y, Sato S, et al. Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. *Stroke* 1995;26:767-73.
- 60 Jakovljevic B, Stojanov V, Paunovic K, Belojevic G, Milic N. Alcohol consumption and mortality in Serbia: twenty-year follow-up study. *Croat Med J* 2004;45:764-8.
- 61 Jamrozik K, Broadhurst RJ, Forbes S, Hankey GJ, Anderson CS. Predictors of death and vascular events in the elderly: the Perth Community Stroke Study. *Stroke* 2000;31:863-8.
- 62 Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. *Stroke* 2000;31:1851-5.
- 63 Kitamura A, Iso H, Sankai T, Naito Y, Sato S, Kiyama M, et al. Alcohol intake and premature coronary heart disease in urban Japanese men. *Am J Epidemiol* 1998;147:59-65.
- 64 Kittner SJ, Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Abbott RD, Havlik RJ. Alcohol and coronary heart disease in Puerto Rico. *Am J Epidemiol* 1983;117:538-50.
- 65 Kivela SL, Nissinen A, Ketola A, Punsar S, Puska P, Karvonen M. Alcohol consumption and mortality in aging or aged Finnish men. *J Clin Epidemiol* 1989;42:61-8.
- 66 Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Fujishima M. The impact of alcohol and hypertension on stroke incidence in a general Japanese population. The Hisayama Study. *Stroke* 1995;26:368-72.
- 67 Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol* 1990;66:1237-42.
- 68 Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk for coronary artery disease hospitalization. *Am J Cardiol* 1997;80:416-20.
- 69 Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hemorrhagic stroke. *Neuroepidemiology* 2002;21:115-22.
- 70 Knuops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 2004;292:1433-9.
- 71 Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Alcohol and mortality: a cohort study of male Japanese physicians. *Int J Epidemiol* 1986;15:527-32.
- 72 Leppala JM, Paunio M, Virtamo J, Fogelholm R, Albanes D, Taylor PR, et al. Alcohol consumption and stroke incidence in male smokers. *Circulation* 1999;100:1209-14.
- 73 Lin Y, Kikuchi S, Tamakoshi A, Wakai K, Kawamura T, Iso H, et al. Alcohol consumption and mortality among middle-aged and elderly Japanese men and women. *Ann Epidemiol* 2005;15:590-7.
- 74 Manttari M, Tenkanen L, Alikoski T, Manninen V. Alcohol and coronary heart disease: the roles of HDL-cholesterol and smoking. *J Intern Med* 1997;241:157-63.
- 75 Marques-Vidal P, Montaye M, Arveiler D, Evans A, Bingham A, Ruidavets JB, et al. Alcohol consumption and cardiovascular disease: differential effects in France and Northern Ireland. The PRIME study. *Eur J Cardiovasc Prev Rehabil* 2004;11:336-43.
- 76 Maskarinec G, Meng L, Kolonel LN. Alcohol intake, body weight, and mortality in a multiethnic prospective cohort. *Epidemiology* 1998;9:654-61.
- 77 Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med* 2003;348:109-18.
- 78 Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth WT Jr, Mittleman MA, et al. Alcohol use and risk of ischemic stroke among older adults: the cardiovascular health study. *Stroke* 2005;36:1830-4.
- 79 Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth WT Jr, Mittleman MA, et al. Alcohol consumption and risk of coronary heart disease in older adults: the Cardiovascular Health Study. *J Am Geriatr Soc* 2006;54:30-7.
- 80 Murray RP, Connett JE, Tyas SL, Bond R, Ekuma O, Silversides CK, et al. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *Am J Epidemiol* 2002;155:242-8.
- 81 Murray RP, Connett JE, Makela P, Rehm J. Difficulty in demonstrating a risk from drinking pattern in fourteen years of coronary heart disease morbidity and mortality: the Lung Health Study. *Addict Behav* 2005;30:875-87.
- 82 Pedersen JO, Heitmann BL, Schnohr P, Gronbaek M. The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality. *Eur Heart J* 2008;29:204-12.
- 83 Rehm JT, Bondy SJ, Sempos CT, Vuong CV. Alcohol consumption and coronary heart disease morbidity and mortality. *Am J Epidemiol* 1997;146:495-501.
- 84 Renaud SC, Gueguen R, Siest G, Salamon R. Wine, beer, and mortality in middle-aged men from eastern France. *Arch Intern Med* 1999;159:1865-70.
- 85 Salonen JT, Puska P, Nissinen A. Intake of spirits and beer and risk of myocardial infarction and death—a longitudinal study in Eastern Finland. *J Chronic Dis* 1983;36:533-43.
- 86 Sankai T, Iso H, Shimamoto T, Kitamura A, Naito Y, Sato S, et al. Prospective study on alcohol intake and risk of subarachnoid hemorrhage among Japanese men and women. *Alcohol Clin Exp Res* 2000;24:386-9.
- 87 Scherr PA, LaCroix AZ, Wallace RB, Berkman L, Curb JD, Cornoni-Huntley J, et al. Light to moderate alcohol consumption and mortality in the elderly. *J Am Geriatr Soc* 1992;40:651-7.
- 88 Shaper AG, Phillips AN, Pocock SJ, Walker M. Alcohol and ischaemic heart disease in middle aged British men. *BMJ* 1987;294:733-7.
- 89 Simons LA, McCallum J, Friedlander Y, Simons J. Alcohol intake and survival in the elderly: a 77 month follow-up in the Dubbo study. *Aust N Z J Med* 1996;26:662-70.
- 90 Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, et al. Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. *Circulation* 2000;102:494-9.
- 91 Suh I, Shaten BJ, Cutler JA, Kuller LH. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group. *Ann Intern Med* 1992;116:881-7.
- 92 Suhonen O, Aromaa A, Reunanen A, Knekt P. Alcohol consumption and sudden coronary death in middle-aged Finnish men. *Acta Med Scand* 1987;221:335-41.
- 93 Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med* 1997;337:1705-14.
- 94 Tolstrup J, Jensen MK, Tjonneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. *BMJ* 2006;332:1244-8.
- 95 Trevisan M, Schisterman E, Mennotti A, Farchi G, Conti S. Drinking pattern and mortality: the Italian Risk Factor and Life Expectancy pooling project. *Ann Epidemiol* 2001;11:312-9.
- 96 Truelsen T, Gronbaek M, Schnohr P, Boysen G. Intake of beer, wine, and spirits and risk of stroke: the Copenhagen city heart study. *Stroke* 1998;29:2467-72.
- 97 Valmadrid CT, Klein R, Moss SE, Klein BE, Cruickshanks KJ. Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. *JAMA* 1999;282:239-46.
- 98 Waskiewicz A, Sygnowska E, Drygas W. Relationship between alcohol consumption and cardiovascular mortality—the Warsaw POLMONICA Project. *Kardiologia* 2004;60:552-62.
- 99 Wellmann J, Heidrich J, Berger K, Doring A, Heuschmann PU, Keil U. Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. *Eur J Cardiovasc Prev Rehabil* 2004;11:48-55.
- 100 Wilkins K. Moderate alcohol consumption and heart disease. *Health Rep* 2002;14:9-24.
- 101 Woo J, Lau EM. Risk factors predisposing to stroke in an elderly Chinese population—a longitudinal study. *Neuroepidemiology* 1990;9:131-4.
- 102 Xu WH, Zhang XL, Gao YT, Xiang YB, Gao LF, Zheng W, et al. Joint effect of cigarette smoking and alcohol consumption on mortality. *Prev Med* 2007;45:313-9.
- 103 Yang T, Doherty TM, Wong ND, Detrano RC. Alcohol consumption, coronary calcium, and coronary heart disease events. *Am J Cardiol* 1999;84:802-6.
- 104 Yuan JM, Ross RK, Gao YT, Henderson BE, Yu MC. Follow up study of moderate alcohol intake and mortality among middle aged men in Shanghai, China. *BMJ* 1997;314:18-23.
- 105 Zhang LF, Zhao LC, Zhou BF, Yang J, Li Y, Wu YF. Alcohol consumption and incidence of ischemic stroke in male Chinese. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004;25:954-7.
- 106 US Government. Alcoholic beverages: dietary guidelines for Americans 2005. US Government Printing Office, 2005.
- 107 Rubin R, Rand ML. Alcohol and platelet function. *Alcohol Clin Exp Res* 1994;18:105-10.
- 108 Mukamal KJ, Ascherio A, Mittleman MA, Conigrave KM, Camargo CA Jr, Kawachi I, et al. Alcohol and risk for ischemic stroke in men: the role of drinking patterns and usual beverage. *Ann Intern Med* 2005;142:11-9.
- 109 National Institute on Alcohol Abuse and Alcoholism. Rethinking drinking: alcohol and your health. What's low risk drinking? 2010. <http://rethinkingdrinking.niaaa.nih.gov/IsYourDrinkingPatternRisky/WhatsLowRiskDrinking.asp>.

- 110 Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011;342:d636.
- 111 Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
- 112 McPherson K. Moderate alcohol consumption and cancer. *Ann Epidemiol* 2007;17:S46-8.
- 113 Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523-8.
- 114 Johansen D, Friis K, Skovenborg E, Gronbaek M. Food buying habits of people who buy wine or beer: cross sectional study. *BMJ* 2006;332:519-22.
- 115 Tjonneland A, Gronbaek M, Stripp C, Overvad K. Wine intake and diet in a random sample of 48763 Danish men and women. *Am J Clin Nutr* 1999;69:49-54.
- 116 Klatsky AL. Alcohol and cardiovascular mortality: common sense and scientific truth. *J Am Coll Cardiol* 2010;55:1336-8.
- 117 Cherpitel CJ. Alcohol, injury, and risk-taking behavior: data from a national sample. *Alcohol Clin Exp Res* 1993;17:762-6.

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